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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/775,678	02/10/2004	Kurt von Figura	S2071-702810	3614

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EXAMINER	
STEADMAN, DAVID J	
ART UNIT	PAPER NUMBER
1656	

NOTIFICATION DATE	DELIVERY MODE
12/28/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/775,678	FIGURA ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *86-96 and 101-123* is/are pending in the application.

4a) Of the above claim(s) *91,106,112,114 and 115* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *86-90,92-96,101-105,107-111,113 and 116-123* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/8/09, 10/1/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Appendix A sequence alignment*.

DETAILED ACTION

Status of the Application

[1] A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/1/09 has been entered.

[2] Claims 86-96 and 101-123 are pending in the application.

[3] Applicants' amendment to the claims, filed on 10/1/09, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[4] Receipt of information disclosure statements filed on 6/8/09 and 10/1/09, is acknowledged.

[5] Applicant's remarks filed on 10/1/09 in response to the final rejection mailed on 4/1/09 have been fully considered and are deemed to be persuasive to overcome at least one of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. Rejections and/or objections previously applied to claims 97-100 are withdrawn solely in view of the instant amendment to cancel these claims.

[6] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Election/Restriction

[7] Claims 91, 106, 112, and 114-115 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

[8] Amended claims 86 and 101 recite inventions that are independent or distinct from the invention originally claimed for the following reasons: Previously, claims 86 and 101 recited the amino acid sequence of SEQ ID NO:2. See the claim listing filed on 1/14/09. Instant claims 86 and 101 have been amended to recite an FGE of "amino acids 34-374 of SEQ ID NO:2, or SEQ ID NO:2, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, or 78". Because each of the amino acid sequences of SEQ ID NO:2, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, and 78 appear to be structurally distinct, claims 86 and 101 reciting each of SEQ ID NO:2, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, and 78 is a separate invention. Claims 86 and 101 reciting each of SEQ ID NO:2, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, and 78 are related as being drawn to sulfatase-producing cells. The related inventions are distinct if: (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, because each of the amino acid sequences of SEQ ID NO:2, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, and 78 appear to be structurally distinct, the inventions as claimed have a materially different design. Furthermore, the inventions as

claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants. Also, because each of the amino acid sequences of SEQ ID NO:2, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, and 78 appear to be structurally distinct, a separate search is required for each of the sequences.

Since applicant has received an action on the merits for the originally presented invention drawn to SEQ ID NO:2, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 86 and 101, reciting SEQ ID NO:46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, or 78 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

[9] Claims 86-90, 92-96, 101-105, 107-111, 113, and 116-123 are being examined on the merits. Claims 86, 96, 101, and 111 are being examined only to the extent the claims read on the elected subject matter, *i.e.,* SEQ ID NO:2 and amino acids 34-374 of SEQ ID NO:2 and Iduronate 2-Sulfatase.

Information Disclosure Statement

[10] All references cited in the information disclosure statements (IDSs) filed on 6/8/09 and 10/1/09 have been considered by the examiner. A copy of Form(s) PTO/SB/08 is attached to the instant Office action.

Claim Objection

[11] Claims 86 and 101 are objected to as reciting non-elected subject matter.

[12] Claims 86, 120, and 121 are objected to in the recitation of "Formylglycine Generating Enzyme of amino acids 34-374 of SEQ ID NO:2". Although the phrase has been interpreted as being an FGE consisting of amino acids 34-374 of SEQ ID NO:2, in the interest of improving claim form, it is suggested that the phrase "Formylglycine Generating Enzyme of amino acids 34-374 of SEQ ID NO:2" be amended to recite, *e.g.*, "Formylglycine Generating Enzyme consisting of amino acids 34-374 of SEQ ID NO:2".

Claim Rejections - 35 USC § 112, Second Paragraph

[13] The rejection of claims 86-90, 92-96, 101-105, 107-111, and 113 as being indefinite in the recitation of "activated form" is maintained for the reasons of record and the reasons set forth below. New claims 116-123 are included in the instant rejection as being dependent from claims 86 and 101. Thus, claims 86-90, 92-96, 101-105, 107-111, 113, and 116-123 are rejected herein. At p. 9 of the instant remarks, applicant argues the claims have been amended to "no longer recite these terms", however, claims 86 and 101 continue to recite "active form". See lines 6 and 15 of claim 86 and lines 6 and 17 of claim 101. Moreover, in view of the deletion of "an activated form" in claims 86 and 101, the phrase "the activated form" in claims 86 and 101 lacks antecedent basis. It is suggested that applicant clarify the meaning of the phrase "activated form" with respect to the recited sulfatase and FGE.

[14] The rejection of claims 101-105, 107-111, and 113 as being indefinite in the recitation of "stringent conditions (6X SSC at 65°C)" is withdrawn in view of the instant amendment to claims 86 and 101 to delete this phrase.

[15] Claim(s) 86-90, 92-96, 98, 101-105, 107-111, and 113 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 86 (claims 87-90, 92-96, 116-117, and 120-121 dependent therefrom) and claims 101 (claims 102-105, 107-111, 113, 118-119, and 122-123 dependent therefrom) are indefinite in the recitation of "the endogenous sulfatase is activated by insertion of a strong promoter" and in the recitation of "the endogenous Formylglycine generating enzyme is activated by insertion of a strong promoter".

First, the phrase is indefinite because it is unclear as to how the endogenous sulfatase of FGE polypeptide is intended to be "activated" by "insertion of a strong promoter".

Second, it is noted that this limitation is a product-by-process type limitation and does not require that the "sulfatase-producing cell" be modified by "insertion of a strong promoter" in the endogenous gene encoding the sulfatase or FGE polypeptide and it is wholly unclear as to how this limitation is intended as limiting an endogenous sulfatase or FGE polypeptide.

Third, it is noted that the term "strong promoter" in claims 86 and 101 is a relative term which renders the claims indefinite. The term "strong promoter" is not defined by

the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

In the interest of advancing prosecution, the phrases "the endogenous sulfatase is activated by insertion of a strong promoter" and "the endogenous Formylglycine generating enzyme is activated by insertion of a strong promoter" are broadly and reasonably interpreted as meaning that "activation" of the endogenous sulfatase or FGE is an effect that can be achieved by insertion of a strong promoter, but not requiring the cell to have an insertion of a strong promoter. It is suggested that applicant clarify the meaning of the noted phrase.

[16] Claim(s) 86-90, 92-96, 98, 101-105, 107-111, and 113 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 86 (claims 87-90, 92-96, 116-117, and 120-121 dependent therefrom) and claims 101 (claims 102-105, 107-111, 113, 118-119, and 122-123 dependent therefrom) are indefinite in the recitation of "expression of the sulfatase is increased" and "expression of the Formylglycine generating enzyme is increased" because it is unclear as to whether "the sulfatase" and "the Formylglycine generating enzyme" in the noted phrases is intended as referring to the endogenous, the exogenous, or both the endogenous and exogenous sulfatase and FGE. In the interest of advancing prosecution, the phrases are broadly and reasonably interpreted as referring to either of

the endogenous, exogenous, or both sulfatase and FGE. It is suggested that applicant clarify the meaning of the noted phrases.

[17] Claim(s) 86-90, 92-96, 98, 101-105, 107-111, and 113 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 86 (claims 87-90, 92-96, 116-117, and 120-121 dependent therefrom) and claims 101 (claims 102-105, 107-111, 113, 118-119, and 122-123 dependent therefrom) are indefinite in the recitation of "exogenous sulfatase, and wherein expression of the sulfatase is increased" and "exogenous Formylglycine generating enzyme...and wherein expression of the Formylglycine generating enzyme is increased". According to a common dictionary definition of "exogenous", the term means "introduced from...outside the organism or system" (Merriam-Webster online dictionary definition of "exogenous"). In view of this definition, the source of the "exogenous sulfatase" and "exogenous Formylglycine generating enzyme" is outside of the cell. As such, it is unclear as to how the cell expresses an exogenous sulfatase and FGE and it is further unclear as to how expression of the "exogenous sulfatase" and "exogenous Formylglycine generating enzyme" can be increased within the cell. It is suggested that applicant clarify the meaning of the claims by, *e.g.*, replacing "exogenous" with "heterologous".

Claim Rejections - 35 USC § 101

[9] Claim(s) 86-90, 93-96, 101-105, 108-111, 113, 116, 118, -123 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims are drawn to sulfatase-producing cells. The claim(s) read on a product of nature and should be amended to indicate the hand of the inventor, e.g., by insertion of "purified" or "isolated" with respect to the claimed cell. See MPEP § 2105.

RESPONSE TO ARGUMENT: At p. 10 of the instant remarks, applicant argues the cells are not products of nature by virtue of claim amendment to require that the endogenous sulfatase and FGE are "activated" by insertion of a strong promoter.

Applicant's argument is not found persuasive. As noted above, the meaning(s) of the phrases "the endogenous sulfatase is activated by insertion of a strong promoter" and "the endogenous Formylglycine generating enzyme is activated by insertion of a strong promoter" is unclear and the phrases are broadly and reasonably interpreted as meaning that activation of the endogenous sulfatase or FGE is an effect that can be achieved by insertion of a strong promoter, but not requiring "insertion of a strong promoter", *e.g.,* into the genome of the cell.

Claim Rejections - 35 USC § 112, First Paragraph

[18] Claims 86-90, 92-96, 101-105, 107-111, 113, and 116-123 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at

the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims are drawn to a sulfatase-producing cell, wherein the ratio of active sulfatase to total sulfatase produced by the cell is increased relative to a cell without the FGE and the cell comprises: 1) an endogenous or exogenous sulfatase, wherein the endogenous sulfatase is "activated by insertion of a strong promoter", wherein the expression of the endogenous or exogenous sulfatase is increased relative to a cell without the "activated form" of the sulfatase and 2) an endogenous or exogenous FGE, wherein the endogenous FGE is "activated by insertion of a strong promoter", wherein the expression of the endogenous or exogenous FGE is increased relative to a cell without the "activated form" of the FGE.

Regarding the "insertion of a strong promoter", the claim does not specify where the "strong promoter" is to be inserted, *i.e.,* there is no indication in the claims that the "strong promoter" is inserted in such a way as to directly increase sulfatase and FGE expression. Instead, the phrase can be broadly and reasonably interpreted as inserting a "strong promoter" such that expression of a polypeptide that upregulates expression of the sulfatase or FGE polypeptide is increased.

Regarding claims 92-94 and 107-109, these claims encompass an embodiment wherein the cell is prokaryotic or non-human, yet the FGE of SEQ ID NO:2 or 95% identical variant is endogenous. The FGE of SEQ ID NO:2 is a human FGE and there is no evidence of record that the FGE of SEQ ID NO:2 or 95% identical variants are endogenous to a cell other than a human cell.

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. Sufficient description to show possession of such a genus "may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus." *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. Possession may not be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural features. *See University of Rochester*, 358 F.3d at 927, 69 USPQ2d at 1895.

MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The specification discloses only the following representative species of the recited genus of sulfatase-producing cells: an isolated host cell transformed with an expression vector encoding a sulfatase polypeptide and encoding the FGE polypeptide of SEQ ID NO:2, 46, 48, 50, 52, 54, 56,

58, 60, 62, 64, 66, 68, 70, 72, 74, 76, or 78, wherein the FGE polypeptide modifies a catalytic cysteine to a formylglycine of the encoded sulfatase such that the ratio of active sulfatase to total sulfatase produced by the cell is increased up to 100% over the ratio of active sulfatase to total sulfatase produced by the cell in the absence of FGE, or an isolated sulfatase-producing that produces an endogenous sulfatase and is transformed with an expression vector encoding the FGE polypeptide of SEQ ID NO:2, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, or 78, wherein the FGE polypeptide modifies a catalytic cysteine to a formylglycine of the encoded sulfatase such that the ratio of active sulfatase to total sulfatase produced by the cell is increased up to 100% over the ratio of active sulfatase to total sulfatase produced by the cell in the absence of FGE. Also, the specification discloses only a single representative species of cells that endogenously express SEQ ID NO:2, *i.e.*, a human cell. In this case, the species encompassed by the genus are widely variant, including species having increased expression of sulfatase and FGE by insertion of a strong promoter, wherein the strong promoter controls expression of any gene and any cell that endogenously expresses SEQ ID NO:2. As such, the genus encompasses widely variant species, wherein the disclosed species fail to reflect the variation among the members of the genus. Given the lack of description of a representative number of peptides, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

Accordingly, for at least the reasons stated above, it is the examiner's position that the specification fails to adequately describe the claimed invention.

RESPONSE TO ARGUMENT: Beginning at p. 10 of the instant remarks, applicant argues the rejection is obviated by amendment. However, at least for the reasons of record and those set forth above, the examiner maintains the position that the specification fails to describe all sulfatase-producing cells as encompassed by the claims.

[19] Claim(s) 86-90, 92-96, 101-105, 107-111, 113, and 116-123 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated sulfatase-producing cell transformed with an expression vector encoding a sulfatase polypeptide and encoding the FGE polypeptide of SEQ ID NO:2, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, or 78, wherein the FGE polypeptide modifies a catalytic cysteine to a formylglycine of the encoded sulfatase such that the ratio of active sulfatase to total sulfatase produced by the cell is increased up to 100% over the ratio of active sulfatase to total sulfatase produced by the cell in the absence of FGE OR an isolated sulfatase-producing that produces an endogenous sulfatase and is transformed with an expression vector encoding the FGE polypeptide of SEQ ID NO:2, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, or 78, wherein the FGE polypeptide modifies a catalytic cysteine to a formylglycine of the encoded sulfatase such that the ratio of active sulfatase to total sulfatase produced by the cell is increased

up to 100% over the ratio of active sulfatase to total sulfatase produced by the cell in the absence of FGE, does not reasonably provide enablement for all sulfatase-producing cells as broadly encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue." *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors considered to be most relevant to the instant rejection are addressed in detail below.

The breadth of the claims: As noted above, the claims are drawn to a sulfatase-producing cell, wherein the ratio of active sulfatase to total sulfatase produced by the cell is increased relative to a cell without the FGE and the cell comprises: 1) an endogenous or exogenous sulfatase, wherein the endogenous sulfatase is "activated by insertion of a strong promoter", wherein the expression of the endogenous or exogenous sulfatase is increased relative to a cell without the "activated form" of the

sulfatase and 2) an endogenous or exogenous FGE, wherein the endogenous FGE is "activated by insertion of a strong promoter", wherein the expression of the endogenous or exogenous FGE is increased relative to a cell without the "activated form" of the FGE.

Regarding the "exogenous" sulfatase and FGE, the term "exogenous" is commonly defined in this context as an object coming from outside of the system and is broadly and reasonably interpreted as encompassing a sulfatase and FGE that are produced *outside* of the cell. Yet the claims require that the exogenous sulfatase and FGE have increased expression, indicating that they are produced within the cell.

Regarding the "endogenous" sulfatase and FGE, as noted above, there is no requirement that cell be modified to insert a "strong promoter" and the phrase "is activated by insertion of a strong promoter" in claims 86 and 101 is interpreted as meaning that activation of the endogenous sulfatase or FGE is an effect that can be achieved by insertion of a strong promoter, but not requiring an active step of insertion of a strong promoter.

Regarding the "insertion of a strong promoter", the claim does not specify where the "strong promoter" is to be inserted and can be broadly and reasonably interpreted as inserting a "strong promoter" such that expression of a polypeptide that upregulates expression of the sulfatase or FGE polypeptide is increased.

Regarding claims 92-94 and 107-109, these claims encompass an embodiment wherein the cell is prokaryotic or non-human, yet the FGE of SEQ ID NO:2 or 95% identical variant is endogenous. The FGE of SEQ ID NO:2 is a human FGE and there is

no evidence of record that the FGE of SEQ ID NO:2 or 95% identical variants are endogenous to a cell other than a human cell.

Also, when interpreted in light of the specification's disclosure at, *e.g.*, p. 39, lines 28-30, the "sulfatase-producing cell" is interpreted as being a cell within a transgenic organism, *e.g.*, a human organism.

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: The state of the art at the time of the invention acknowledges methods for increasing expression of a desired protein by recombinantly expressing the desired protein using an expression vector. However, there is no disclosure in the prior art of increasing expression of a sulfatase and FGE in a cell by "insertion of a strong promoter" in a cell, including insertion of a "strong promoter" controlling expression of polypeptides that regulate expression of a sulfatase or FGE.

Regarding transgenic cells, the prior art acknowledges the unpredictability of gene transfer in an organism. See, *e.g.*, Juengst (*BMJ* 326:1410-1411, 2003).

The amount of direction provided by the inventor and The existence of working examples: The specification discloses the following working examples of a sulfatase-producing cell as encompassed by the claims, *i.e.*, transformation of a host cell with an expression vector encoding the sulfatase and FGE polypeptide of SEQ ID NO:2, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, or 78, or transformation of a host cell expressing an endogenous sulfatase with an expression vector encoding the FGE polypeptide SEQ ID NO:2, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, or 78.

The specification fails to provide any guidance for insertion of a "strong promoter" for increasing expression of a sulfatase or FGE polypeptide.

The specification fails to provide a working example of a transgenic organism comprising a sulfatase-producing cell as encompassed by the claims. Further, the specification fails to provide any specific guidance for modifying a cell to achieve overexpression of a sulfatase and an FGE.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: It was not routine in the art at the time of the invention to insert any "strong promoter" into any region of a host cell's genome to screen for those that have the ability to increase sulfatase or FGE protein expression, including a whole transgenic organism.

Thus, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation that is required, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired characteristics is unpredictable and the experimentation left to those skilled in the art is

unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

RESPONSE TO ARGUMENT: Initially, it should be noted applicant, in noting the Office action mailed on 4/1/09 states the specification is enabling for "a sulfatase-producing cell", mischaracterizes the examiner's statement. The Office action actually states, "the specification, while being enabling for an *isolated* sulfatase-producing cell".

Beginning at p. 11 of the instant remarks, applicant argues the rejection is obviated by amendment. However, at least for the reasons of record and those set forth above, the examiner maintains the position that the specification fails to enable the full scope of sulfatase-producing cells.

Claim Rejections - 35 USC § 102/103

[20] The rejection of claims 86-90, 92, 101-105, and 107 under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Szameit as evidenced by Fang and GenBank AJ131525 is withdrawn in view of the instant amendment to require the sulfatase-producing cell express an FGE of amino acids 34-374 of SEQ ID NO:2 or SEQ ID NO:2 or variants thereof having at least 95% identity to amino acids 34-374 of SEQ ID NO:2 or SEQ ID NO:2. Although the AtsB polypeptide of *Klebsiella pneumoniae* is an FGE, it is not an FGE of amino acids 34-374 of SEQ ID NO:2 or SEQ ID NO:2 or variants thereof having at least 95% identity to

amino acids 34-374 of SEQ ID NO:2 or SEQ ID NO:2 as required by the claims. See Appendix A sequence alignment.

[21] Claim(s) 86-90, 93-96, 101-105, 108-111, 113, 116-119, and 122-123 are rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Rommerskirch (reference U of Form PTO-892 mailed on 9/17/07) as evidenced by Dierks (cited in the IDS filed on 2/28/05) and as evidenced by Wraith (*Hum. Genet.* 87:205-206, 1991; hereafter referred to as "Wraith").

CLAIM INTERPRETATION: The claims have been broadly, but reasonably interpreted as noted above, particularly with respect to the phrase "is activated by insertion of a strong promoter" with respect to the endogenous sulfatase and FGE as meaning that activation of the endogenous sulfatase or FGE is an effect that can be achieved by insertion of a strong promoter, but not requiring the cell have an insertion of a strong promoter and the lack of clarity regarding the meaning of "activated form" with respect to a sulfatase and FGE. Regarding claims 117, 119, and 123, it is acknowledged the claims recite "exogenous" with respect to the FGE. However, the phrase "exogenous" in the claims is interpreted as a product-by-process limitation and does not distinguish an FGE from one that is endogenous. Put another way, the phrase "exogenous", while implying the process by which the polypeptide is produced, does not limit the structure of the recited FGE such that it is distinguished from an "endogenous" FGE.

The reference of Rommerskirch teaches a comparison of steroid sulfatase (STS) mRNA in control human fibroblasts and human chromosome X-linked-ichthyosis fibroblasts (p. 2562, Figure 1). According to the reference, "[i]n total RNA of controls…the STS probe detects RNA species…[i]n total RNA from fibroblasts carrying a deletion of the STS gene (X-linked ichthyosis), none of the STS RNA species is detectable" (p. 2562, column 1, bottom and p. 2562, column 2, top). The reference teaches a comparison of STS enzymatic activities in control fibroblasts and chromosome X-linked-ichthyosis fibroblasts (p. 2563, Table 3). According to Table 3, the STS activity in control fibroblasts is 1.4 nmol/hr/mg and 0.05 nmol/hr/mg for chromosome X-linked-ichthyosis fibroblasts (p. 2563). The results of Rommerskirch demonstrate that normal human fibroblasts have increased expression of STS relative to chromosome X-linked-ichthyosis fibroblasts. Rommerskirch further teaches a comparison of STS enzymatic activities in control fibroblasts and multiple sulfatase deficiency (MSD) fibroblasts (p. 2563, Table 3). According to Table 3, the STS activity in control fibroblasts is 1.4 nmol/hr/mg and <0.05 nmol/hr/mg for MSD fibroblasts (p. 2563), wherein 1.4 nmol/hr/mg is an increase of "at least 100%" over <0.05nmol/hr/mg.

According to evidentiary reference Dierks, "C_α-formylglycine (FGly) is the catalytic residue in the active site of eukaryotic sulfatases. It is posttranslationally generated from a cysteine in the endoplasmic reticulum. The genetic defect of FGly formation causes multiple sulfatase deficiency (MSD)" (p. 435, "Summary" section). Dierks provides evidence that MSD fibroblasts are defective in FGE activity (p. 440, Table 2), wherein complementation of MSD fibroblasts with DNA encoding FGE

enhanced STS activity, albeit to a lower level than normal fibroblasts. As shown by evidentiary reference Dierks, normal human fibroblasts appear to have increased expression of catalytically active FGE relative to MSD fibroblasts. Since the normal fibroblasts and the MSD fibroblasts are both fibroblasts, they are considered to be of the same cell type. Also, Dierks discloses that human FGE (p. 437, Figure 3), which is 100% identical to SEQ ID NO:2 herein, is expressed in fibroblasts (p. 437, column 2, bottom) and has a domain 3 sequence NH_3-RVKKGGS-COO^- (p. 437, Figure 3, amino acids 327 to 333) and thus satisfies the FGE structural requirements of claim 113.

Regarding claims 96 and 111, evidentiary reference Wraith teaches cultured fibroblasts with a complete deletion of the iduronate-2-sulfatase (IDS) gene (p. 205, abstract and p. 206, Figure 1 caption), where the normal fibroblasts of Rommerskirch and the fibroblasts of Wraith are both of the same cell type and since an IDS gene is deleted in the fibroblasts of Wraith, the normal fibroblasts of Rommerskirch necessarily have increased expression of iduronate-2-sulfatase relative to the fibroblasts of Wraith, thus satisfying the limitations of claims 96 and 111.

The normal human fibroblasts of Rommerskirch anticipate the claimed sulfatase-producing cell since: 1) Rommerskirch teaches normal human fibroblasts have increased expression of STS (a sulfatase) relative to chromosome X-linked-ichthyosis fibroblasts, *i.e.,* normal human fibroblasts have increased expression of sulfatase as compared to expression in the same cell type without the "activated form" of the sulfatase; 2) Rommerskirch teaches normal human fibroblasts have increased STS activity relative to MSD fibroblasts, which, as evidenced by Dierks, are defective in FGE

activity and thus normal human fibroblasts have increased expression of FGE relative to MSD fibroblasts", *i.e.,* normal human fibroblasts have increased expression of FGE as compared to expression in the same cell type without the "activated form" of the FGE; 3) As evidenced by Dierks, human FGE is expressed in fibroblasts and human FGE is 100% identical to SEQ ID NO:2 herein; and 4) MSD fibroblasts are defective in FGE and exhibit <0.05nmol/hr/mg STS activity relative to normal human fibroblasts that produce FGE and exhibit 1.4 nmol/hr/mg STS activity, which is evidence that normal human fibroblasts have active sulfatase activity that is 100% greater than sulfatase activity of human fibroblasts in the absence of FGE. This anticipates claims 86-90, 93-96, 101-105, 108-111, 113, 116-119, and 122-123 as written.

RESPONSE TO ARGUMENT: Beginning at p. 13 of the instant remarks, applicant argues the cell of Rommerskirch is not encompassed by the claims.

Applicant's argument is not found persuasive. As noted above, in view of a broad and reasonable interpretation of the claims, the normal human fibroblast of Rommerskirch is considered to be encompassed by the claims.

Conclusion

[22] Status of the claims:

- Claims 86-96 and 101-123 are pending.
- Claims 91, 106, 112, and 114-115 are withdrawn from consideration.
- Claims 86-90, 92-96, 101-105, 107-111, 113, and 116-123 are rejected.

- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/David J. Steadman/
Primary Examiner, Art Unit 1656

APPENDIX A

Query sequence 1

>AMINO ACIDS 34-374 OF SEQ ID NO:2
SQEAGTGAGAGSLAGSCGCGTPQRPGAHGSSAAAHRYSREANAPGPVPGERQLAHSKMVP
IPAGVFTMGTDDPQIKQDGEAPARRVTIDAFYMDAYEVSNTEFEKFVNSTGYLTEAEKFG
DSFVFEGMLSEQVKTNIQQAVAAAPWWLPVKGANWRHPEGPDSTILHRPDHPVLHVSWND
AVAYCTWAGKRLPTEAEWEYSCRGGLHNRLFPWGNKLQPKGQHYANIWQGEFPVTNTGED
GFQGTAPVDAFPPNGYGLYNIVGNAWEWTSDWWTVHHSVEETLNPKGPPSGKDRVKKGGS
YMCHRSYCYRYRCAARSQNTPDSSASNLGFRCAADRLPTMD

Query sequence 2

>AtsB of Klebsiella pneumoniae
MLNIAALRQQQIPLAAEPRSPVPPHILMKPIGPACNLACRYCYYPQDETPVNKMDDARLE
QFIRRYIAAQPAGAREINFVWQGGEPLLAGLSFYKKALALQARYAPDGVTISNSLQTNGT
LINDAWCRLFREHGFIIGLGLEGNEALQDYHRPDKRGRSTWSAALRGIDLLHQHQVDFNL
LVVVHNEMAAHAAAIYVKLVGLGARYLQPQPLMSEGAALAEGYQLSADNWGRFMVGIWKQ
WRKRCDRGRVFVINIEQAWAQYFTHTSGSCVHSARCGSNLVMESDGQLYACDHLLNTEHR
LGRLDEQTLAAAVDASVQLPFGQQKSLRRECQTCSVKMVCQGGCPAHLNAAGNNRLCGGY
YRFFSDILAPLRPFSRDLNGLKAWRAAFVGTAHTA

Full-length alignment between two sequences

```
>>AtsB of Klebsiella pneumoniae                              (395 aa)
 s-w opt:  74  Z-score: 79.2  bits: 23.3 E(): 0.013
Smith-Waterman score: 74;  21.849% identity (24.528% ungapped) in 119 aa overlap (158-273:18-126)

       130       140       150       160       170       180
AMINO  MLSEQVKTNIQQAVAAAPWWLPVKGANWRHPEGP-DSTILHRPDHPVLHVSWNDAVAYCT
                                        :..:    :: .: :.     : :  ::
AtsB                MLNIAALRQQQIPLAAEPRSPVPPHILMKPIGPAC----NLACRYCY
                           10        20        30            40

        190       200       210       220       230       240
AMINO  WAGKRLPTEAEWEYSCRGGLHNRLFPWGNKLQPKGQHYAN-IWQGEFPVTNTGEDGFQGT
       .   . :..   .   .  ..  .       :: : .  : .::: :.  .: . .. .
AtsB   YPQDETPVNKMDDARLEQFIRRYI-----AAQPAGAREINFVWQGGEPLL-AGLSFYKKA
            50        60                70        80        90

          250       260       270       280       290       300
AMINO  APVDA-FPPNGYGLYNIVGNAWEWTSDWWTVHHSVEETLNPKGPPSGKDRVKKGGSYMCH
         ..: . :.:  . : . .     .: :
AtsB   LALQARYAPDGVTISNSLQTNGTLINDAWCRLFREHGFIIGLGLEGNEALQDYHRPDKRG
       100       110       120       130       140       150
```